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EFFECT OF TETHELIN ON EXPERIMENTAL TUBERCULOSIS *

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The treatment of tuberculosis may be considered from 2 important standpoints. The one, a direct therapy, is concerned mainly in influencing the tubercle bacillus directly, that is, by killing it — a tuberculocide — or by inhibiting its growth, thus considering the influence of the host as merely passive. The other, an indirect therapy, is concerned mainly in influencing the host, which effect may be observed in the tubercle, and by this means having an indirect influence on the tubercle bacillus invading the host. Of course an ideal therapeutic agent would be one which would have both a favorable direct and a favorable indirect action at the same time. It is conceivable that a therapeutic agent may have a favorable direct action and still its unfavorable indirect action may remove it from practical consideration or vice versa. Up to the present time the scientific world has not accepted, on account of lack of conclusive evidence, a single therapeutic agent of the direct type as being of any practical value. On the other hand any number of indirect therapeutic agents are accepted as matter of fact even though the evidence of their value is based mainly on empiric clinical observations. Of these may be mentioned such agents as foods (fats, that is, butter, cod liver oil, etc.), sunlight, fresh air, absolute rest, intestinal antiseptics, etc. On account of the success thus far obtained with the indirect therapeutic procedures it is naturally to be expected that this field will be far more productive than the direct, and in the zealous search for the latter the former should not be left out of consideration by the investigator searching for therapeutic agents. It was with a view to finding an additional indirect therapeutic agent which might be of practical value that the following investigations were carried out.

Within the past year Robertson[1] has presented the scientific world a new substance, which he terms 'tethelin' (from τεθηλώς, growing), precipitated from the alcoholic extract of dried anterior lobes of ox

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* Received for publication April 12, 1917.

[1] Jour. Biol. Chem., 24, 1916, p. 392. Ibid., p. 409.

pituitaries by the addition of 1½ volumes of dry ether. This precipitate from the constancy of its nitrogen and phosphorus content appears to be a chemical unit, is markedly hygroscopic, soluble in water (to the extent of about 5%), ethyl alcohol, ethyl ether, chloroform, and carbon tetrachlorid, but is insoluble in a mixture of 1 part by volume absolute alcohol and 1½ parts of dry ether. The average yield is about 10 mg. tethelin from each anterior lobe of ox pituitary. Although containing a iminazolyl group similar to the active substance of the posterior lobe of the pituitary body, it does not possess the characteristic physiologic activity of these substances, relatively large doses administered intravenously to rabbits producing only a slight, transient fall in blood pressure and no diuresis. The effect of tethelin on the growth of white mice resembles in every particular the effects of the administration of the whole anterior lobe with an initial (preadolescent) retardation and final (postadolescent) acceleration. Tethelin-fed mice are more compact in form and build than normal animals of the same age and their coats retain the glossy, silky appearance of the coats of young animals.

Robertson and Burnett[2] found that the hypodermic administration of tethelin increases markedly the rate of growth of the primary, and the tendency to form metastasis in rats inoculated with carcinoma while other alcohol-soluble extractive of the anterior lobe of the pituitary body, with the exception of the lecithin fraction, exerted no appreciable influence. Lecithin fractions from eggs had no such effect.

The following observations by Robertson,[3] however, seemed to indicate especially that tethelin would be productive of results as an indirect therapeutic agent in tuberculosis. He found that mice suffering from inanition and given 10 mg. of tethelin hypodermically regained weight following admission of food much more rapidly than controls not receiving tethelin, and that tissue repair, as evidenced by the healing of granulating wounds in mice, was accelerated by tethelin. If, for instance, tethelin could hasten the healing of tubercles in stimulating scar tissue formation or granulating bleeding denuded areas produced by the tuberculosis or even aid in stimulating weight increase in certain cases of tuberculous inanition its use would certainly be a valuable adjunct to the procedures at present available in treating tuberculosis.

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[2] Jour. Exper. Med., 23, 1916, p. 631.

[3] Jour. Am. Med. Assn., 1916, 66, p. 1009.

To determine the value of an indirect therapeutic agent, in which class tethelin must be considered, practically 2 routes of investigation are open: to note the effect of treatment in practical doses on the rate of development of tuberculosis in the experimental animal, and to determine the effect of treatment on the local tubercle which is the true index of indirect therapeutic action.

EFFECT OF TETHELIN ON THE RATE OF DEVELOPMENT OF TUBERCULOSIS

In this series are included 8 male guinea-pigs of approximately the same weight. All were infected by the subcutaneous injection in the left lower quadrant of the abdomen, of 0.05 mg. of an emulsion of a virulent tubercle bacillus, No. 1305, the culture on glycerin agar being about 2 months old. Four of these pigs were used as controls not receiving tethelin and 4 of them received tethelin in 25 mg. doses in 0.5 c.c. sterile salt solution on alternate days for 18 days beginning on the day of infection. At the end of 2½ months those not having died before this time were killed and examined for the extent of involvement with tuberculosis. The guinea-pigs were weighed at frequent intervals during the course of the experiment, but no significant difference between the controls and test pigs was obtained.

My thanks are due Prof. T. Brailsford Robertson for supplying the tethelin used in these experiments and for his cooperation.

CONTROL ANIMAL 1.—Examination after the animal was killed, 2½ months after infection, revealed a small nodule at the site of injection; the local glands were slightly enlarged and caseous, the retroperitoneal glands were enlarged and hard, the spleen was about 5 times normal size and full of small necrotic areas, the liver revealed nothing macroscopically, the peribronchial and tracheal glands were markedly enlarged and hard and the lungs contained a number of small tubercles. Tuberculosis + + +.*

CONTROL ANIMAL 2.—Examination after the animal was killed, 2½ months after infection, revealed nothing at the site of injection, but small caseous local glands and large hard retroperitoneal glands; the spleen was 10 times normal size and full of large necrotic areas; the liver contained a few necrotic areas; the tracheal and peribronchial glands were much enlarged and hard; and the lungs contained a few isolated tubercles. Tuberculosis + + +.

CONTROL ANIMAL 3.—Examination after the animal was killed, 2½ months after infection, revealed on section a local discharging ulcer at the site of injection, large caseous local glands, and small hard retroperitoneal glands; the spleen was 5 times normal size and contained a few large solitary necrotic areas; the liver appeared normal; the tracheal and peribronchial glands were large and hard; and the lungs contained a few isolated tubercles. Tuberculosis + +.

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* This marking is given to designate the impression of the amount of tuberculosis noted.

CONTROL ANIMAL 4—.Examination following the death of the animal, 2 months after infection, revealed a small nodule at the site of injection, fairly large caseous local glands, and large hard retroperitoneal glands; the spleen was about 10-15 times normal size and was full of miliary tubercles; the liver contained a few necrotic areas; the peritoneal cavity contained a bloody fluid; the tracheal and peribronchial glands were large and hard; and the lungs contained a few isolated tubercles. Tuberculosis + + +.

TREATED ANIMAL 1.—Examination after the animal was killed, 2½ months after infection and beginning of treatment with tethelin, revealed a small nodule at the site of injection, fairly large caseous local glands, fair-sized hard retroperitoneal glands; the spleen was about 10 times normal size and full of small necrotic areas; the liver contained a few necrotic areas; the tracheal and peribronchial glands were markedly enlarged and hard; and the lungs contained a few isolated tubercles. Tuberculosis + + +.

TREATED ANIMAL 2.—Examination after the animal was killed, 2½ months after initiation of the experiment, revealed a small local ulcer at the site of injection; the local glands were large and caseous; the retroperitoneal glands were not very large but hard; the spleen was about 5 times normal size and contained a few large necrotic areas; the liver appeared normal; the tracheal and peribronchial glands were markedly enlarged and hard; and the lungs contained a few isolated tubercles. Tuberculosis + +.

TREATED ANIMAL 3.—Examination after the animal was killed, 2½ months after initiation of the experiment, revealed a small local nodule, large caseous local glands, and large hard retroperitoneal glands; the spleen was full of small necrotic areas and about 10 times normal size; the liver contained a few necrotic areas; the tracheal and peribronchial glands were large and hard; and the lungs revealed nothing macroscopically. Tuberculosis + + +.

TREATED ANIMAL 4.—Examination after the animal was killed, 2½ months after infection and beginning treatment with tethelin, revealed a small local nodule and large caseous local glands; the retroperitoneal glands were of fair size and hard; the spleen was enlarged about 10 times normal size and contained numerous necrotic areas; the liver was practically normal; the tracheal and peribronchial glands were large and hard; and the lungs contained a few isolated tubercles. Tuberculosis + + +.

EFFECT OF TETHELIN ON THE DURATION OF LIFE

In this series are included 8 male guinea-pigs of approximately the same weight; all were infected by the subcutaneous injection in the lower left quadrant of the abdomen of 0.5 mg. of an emulsion of virulent human tubercle bacilli No. 7, the culture on Petroff medium[4] being about 1½ months old, freshly isolated from tuberculous sputum.

Four of these pigs were used as controls not receiving tethelin and 4 of them received 0.5 c.c. salt solution containing 25 mg. tethelin on alternate days for 16 days, beginning on the day of infection. The pigs were allowed to die a natural death, the duration of life and the extent of the tuberculosis at the time of death were noted.

[4] Jour. Exper. Med., 1915, 21, p. 38.

CONTROL ANIMAL 1.—Examination following death of animal, 62 days after infection, revealed a local ulcer; the inguinal glands were enlarged and caseous; the spleen was 5 times normal size and full of necrotic areas; the retroperitoneal glands were large and hard; the liver was large and necrotic; the tracheal and peribronchial glands were large and hard; and the lungs contained a few isolated tubercles. Tuberculosis + + + +.

CONTROL ANIMAL 2.—Examination following the death of the animal, the 136th day after infection, revealed a healed local site, slightly enlarged local glands, no enlarged retroperitoneal glands; the spleen was about 10 times normal size and full of miliary necrotic areas; the liver was full of massive necrotic areas; the tracheal and peribronchial glands were large and hard; and the lungs contained numerous fibrocaseous tubercles. Tuberculosis + + +.

CONTROL ANIMAL 3.—Examination following the death of the animal, the 105th day after infection revealed no local site but large caseous local glands; the retroperitoneal glands were large and hard; the spleen was about 5 times normal size and was full of necrotic areas; the liver was full of massive necrotic areas; the tracheal and bronchial glands were large and hard; and the lungs contained numerous fibrocaseous tubercles. Tuberculosis + + +.

CONTROL ANIMAL 4.—Examination following the death of the animal on the 82nd day after infection revealed a healed local site, large caseous local glands, and large retroperitoneal glands; the spleen was about 5 times normal size and full of necrotic areas; the liver was full of massive necrosis; the tracheal and bronchial glands were large and hard; and the lungs contained a few tubercles. Tuberculosis + + +.

TREATED ANIMAL 1.—Examination following the death of the animal, 57 days after infection, revealed a local discharging ulcer; the local glands were large and caseous; the retroperitoneal glands were slightly enlarged and hard; the spleen was 10 times normal size and full of diffuse necrotic masses; the liver was full of necrotic areas; the tracheal and peribronchial glands were slightly enlarged and hard; and the lungs contained numerous small tubercles. Tuberculosis + + +.

TREATED ANIMAL 2.—Examination following the death of the animal, 110 days after infection, revealed a healed local site; the local glands were large and caseous; the retroperitoneal glands were large and hard; the spleen was 10 times normal size and full of necrotic areas; the liver was diffusely necrotic; the tracheal and peribronchial glands were large and hard; and the lungs contained many tubercles. Tuberculosis + + +.

TREATED ANIMAL 3.—Examination following the death of the animal, 80 days after infection, revealed a healed local site; the local glands were slightly enlarged and hard; the retroperitoneal glands were large and hard; the spleen was enlarged 20 times and was full of diffuse necrosis; the liver revealed no tuberculosis; the tracheal and peribronchial glands were markedly enlarged; and the lungs contained numerous tuberculous foci. Tuberculosis + + +.

TREATED ANIMAL 4.—Examination following the death of the animal, on the 78th day after infection, revealed a healed local site; the local glands were large and hard; the retroperitoneal glands were large and hard; the spleen was enlarged 5 times and was full of diffuse necrosis; the liver contained a few small necrotic areas; the tracheal and peribronchial glands were markedly enlarged and hard; the lungs contained a few tuberculous foci. Tuberculosis + +.

As a result of these experiments it seems justifiable to conclude that tethelin in the manner (subcutaneous) and doses (25 mg. on alternate days for 16-18 days) given had no appreciable effect on the progress of tuberculosis in the guinea-pigs or on the duration of life of the animals.

EFFECT OF TETHELIN ON THE LOCAL TUBERCLE

Since the tubercle is the expression of the body's fight against tuberculosis it would seem that an indirect therapeutic agent if it is to be considered of any value in tuberculosis must express itself in some action on the tubercle. In order to study this action experimentally, it is necessary that a standard tubercle be produced which is easily observed at frequent intervals and possible of duplication under the same conditions of experiment. In experiments to be published later, it has been found that such tubercles may be produced by the intracutaneous injection of standard amounts of dead tubercle bacilli into the abdomen of guinea-pigs, which had previously received a primary injection of either dead or living tubercle bacilli. There was a slight difference in the tubercles thus produced in different guinea-pigs, but in the same guinea-pig it was possible to duplicate, with regard to development and rupture, the tubercle at least 3 times. Thus if the 1st intracutaneous tubercle was used as the control, the effect of the

TABLE 1

DEVELOPMENT AND RECESSION OF NORMAL TUBERCLE IN GUINEA-PIGS *

Days	1A	1B	2A	2B	3A	3B	4A
2	0.17	0.37	0.16	0.28	0.18	0.31	0.23
4	0.30	0.42	0.23	0.40	0.26	0.36	0.35
6	0.34	0.43	0.31	0.40	0.33	0.37	0.39
8	0.34	(0.38)	(0.27)*	(0.38)	(0.30)*	(0.36)*	(0.35)
10	(0.26)	(0.28)	(0.23)	(0.20)	(0.25)	(0.25)	(0.27)
12	(0.22)	(0.28)	(0.13)	(0.20)	(0.22)	(0.22)	(0.23)
14	(0.21)	(0.26)	(0.12)	(0.16)	(0.16)	(0.19)	(0.20)
16	(0.20)	(0.18)	(0.12)	0.10	(0.15)	0.14	0.20
18	(0.15)	(0.16)	(0.11)	0.09	0.15	0.10	0.14
20	(0.14)	0.14	0.10	0.09	0.12	0.08	0.12
22	(0.13)	0.13	0.09	0.08	0.10	0.08	0.10
28	0.08	0.09	0.06	0.06	0.07	0.06	0.08
Weight at beginning of exper.	905	850	850	795	990	990	795

* The (b) tubercles were initiated 23 days after injecting the bacilli intracutaneously for the (a) tubercles.

Guinea-pigs 1, 2, 3, and 4 were given the previous subcutaneous injection of living avirulent bacilli, while 5, 6, 7, and 8 were given the dead bacilli.

The diameter of the tubercles though taken are of no especial significance and are therefore omitted.

The numeral in parentheses signifies that the tubercle has ruptured and is discharging. The asterisk after such numeral indicates that only 1 tubercle has ruptured at the time recorded.

therapeutic agent to be tested could be gauged on the 2nd or 3rd intracutaneous tubercle produced.

In this series of experiments are included 8 male guinea-pigs, 4 of which (5, 6, 7, and 8) had been given an initial injection of dead human tubercle bacilli equivalent to 0.2 mg. of water free (dried at 100 C. for analysis) residue 52 days previous to initiation of the test, and 4 of which (1, 2, 3, and 4) had been given an initial injection of 5 mg. of living avirulent human tubercle bacilli 221 days before the initiation of this test. Two of the former set and 2 of the latter set of pigs were used as controls (that is, carried through entirely without treatment) while the remaining 2 of each set were used to gauge the effect of the tethelin. In all of them, however, the 1st intracutaneous tubercles, of which there were 2 produced in each animal (the mean of these being given in the tables), were used as the controls without treatment with tethelin. The intracutaneous tubercles were produced by the injection of 0.1 c.c. of an emulsion of dead human tubercle bacilli containing an equivalent of 0.11 mg. of bacillary bodies dried at 100 C. (The dry weight was used merely as the gauge of amounts.)

TABLE 1—*Continued*

DEVELOPMENT AND RECESSION OF NORMAL TUBERCLE IN GUINEA-PIGS *

4B	5A	5B	6A	6B	7A	7B	8A	8B
0.28	0.17	0.30	0.19	0.28	0.29	0.34	0.20	0.32
0.39	0.29	0.42	0.29	0.36	0.42	0.42	0.27	0.37
0.42	0.29	(0.40)*	0.33	0.42	0.42	0.42	0.29	0.38
(0.38)	(0.25)*	(0.32)	(0.26)	(0.32)	(0.42)*	(0.44)	(0.25)*	(0.31)
(0.21)	(0.25)	(0.21)	(0.19)	(0.24)	(0.28)	(0.36)	(0.19)	(0.24)
(0.17)	(0.23)	(0.17)	(0.15)	(0.18)	(0.24)	(0.30)	(0.15)	(0.17)
0.12	(0.22)	(0.16)	(0.13)	(0.15)	(0.21)	(0.26)	(0.13)	(0.17)
0.10	(0.21)	0.11	0.13	0.10	(0.18)	(0.21)	(0.13)	(0.11)
0.08	0.20	0.09	0.11	0.08	(0.17)	(0.17)	(0.12)	0.09
0.08	0.20	0.07	0.10	0.07	0.15	0.14	0.10	0.09
0.07	0.09	0.06	0.08	0.06	0.12	0.11	0.10	0.08
0.06	0.07	0.04	0.06	0.05	0.08	0.09	0.08	0.06
825	765	740	710	740	655	655	680	655

The figures in the tables are given in centimeters of actual tubercle thickness as measured by calipers graduated in one hundredth of a centimeter, the figure being obtained by subtracting from the mean figure, obtained by measuring the tubercle plus twice the skin thickness, the thickness of the double normal skin as control in the vicinity of the tubercle, but far enough away not to be influenced by it. The 8 animals referred to by number in Table I were used for the experiments in Tables 2 and 3. In Table 2 it is noted that one half of the animals (the even numbers) were treated with tethelin while the other half (odd numbers) were not treated during observation of the tubercle. In Table 3 the treatment with tethelin was continued (with the even numbers), while the wound healing was studied in the entire series.

Table 1 shows 2 important facts: The development and recession, including healing of the tubercle, produced by the intracutaneous injection of dead human tubercle bacilli in previously sensitized guinea-pigs, occurs in a fairly definite curve form, although there are distinct variations in size of the individual tubercles thus produced; and the tubercle ruptures in these animals at a fairly definite time — in the

TABLE 2

DEVELOPMENT AND RECESSION OF TUBERCLE UNDER TREATMENT WITH TETHELIN *

Days	1	2	3	4	5	6	7	8
2	0.20	0.27	0.27	0.24	0.18	0.17	0.30	0.22
4	0.29	0.33	0.31	0.36	0.26	0.31	0.36	0.24
6	0.34	0.36	0.37	0.42	0.33	0.34	0.38	0.28
8	0.35	(0.26)	(0.38)	(0.35)	(0.26)	(0.24)	(0.30)	0.28
10	(0.28)	(0.16)	(0.19)	(0.18)	(0.23)	(0.18)	(0.21)	(0.20)
12	(0.15)	(0.14)	(0.16)	(0.16)	(0.21)	(0.13)	(0.17)	(0.18)
14	(0.13)	(0.12)	0.12	(0.12)	(0.20)	(0.12)	(0.16)	(0.15)
16	(0.13)	(0.10)	0.11	0.10	0.08	(0.11)	(0.14)	(0.13)
18	(0.11)	0.07	0.10	0.08	0.06	0.09	(0.13)	(0.11)
20	0.09	0.06	0.08	0.06	0.05	0.08	0.12	0.08
22	0.08	0.05	0.07	0.06	0.05	0.07	0.09	0.07
28	0.04	0.03	0.05	0.04	0.03	0.05	0.06	0.04
Weight in grams	905	825	1050	850	765	795	710	655

* These intracutaneous tubercles were initiated 16 days after tubercle (b) of Table 1 had been initiated and the figures are the mean of readings of 2 tubercles, after deducting the double skin thickness as in Table 1. The even number animals (2, 4, 6, and 8) received 25 mg. doses of tethelin in 0.5 c.c. physiologic salt solution practically daily from 4 days previous to the initiation of the tubercle until 18 days after (a total of 0.4 gm. to each animal) when it was further continued as stated in footnote to Table 3.

The numbers of the animals correspond to those in Table 1.

TABLE 3

HEALING OF DEEP SKIN WOUNDS UNDER TETHELIN TREATMENT *

Days	1	2	3	4	5	6	7	8
0	0.45	0.45	0.47	0.46	0.46	0.46	0.48	0.44
1	0.40	0.34	0.43	0.44	0.42	0.48	0.47	0.43
2	0.35	0.34	0.48	0.45	0.39	0.47	0.47	0.42
4	0.34	0.33	0.47	0.44	0.40	0.42	0.41	0.40
6	0.28	0.32	0.41	0.43	0.35	0.37	0.38	0.32
8	0.25	0.27	0.35	0.34	0.20	0.15	0.21	0.18
10	—†	0.18‡	0.29	0.25‡	0.16‡	0.13	0.12	0.15‡
12		—†	—†	0.10‡	—†	—†	—†	0.09‡
Weight at end of exper. in grams	825	825	1080	850	710	825	680	680

* These animals are a continuation of the ones referred to in Tables 1 and 2, the numbers corresponding, and the administration of tethelin was continued to the even numbers in 25 mg. doses daily in 0.5 c.c. physiologic salt solution (having been given a total of 0.4 gm. in 22 days) for another 10 days, an additional total of 0.25 gm. more.

These figures are diameter of lesion in centimeters, a mean of 2 figures, that is, 2 lesions; wherever the lesion was irregular in shape the mean of the longest and shortest diameters is used as the individual reading of a lesion.

The holes were made by lifting up a double fold of skin on the abdomen of the guinea-pig after shaving and cleaning thoroughly and punching a double hole through the entire by means of a sharp paper punch making round perforations about 0.4-0.5 cm. in diameter.

† A dash indicates the lesion is entirely healed and only a contracted scar tissue remains.

‡ A double dagger after a figure indicates that only one lesion is healed.

above experiments the 8th or 10th day (as will be shown in a subsequent paper, this rupture may be influenced by at least 1 factor, the nutrition of the animal).

Table 2 shows that the administration of tethelin in 25 mg. doses daily to 650-850 gm. sensitized guinea-pigs had no influence either on the development or recession (and healing) of the tubercle or on its rupture.

Table 3 shows that tethelin in 25 mg. doses daily given to 680-850 gm. sensitized guinea-pigs had no appreciable effect on the healing of deep wounds.

DISCUSSION

Robertson[3] obtained a hastening of wound healing in mice weighing about 20-25 gm. after administration of 10 mg. of tethelin, which would correspond to a dosage of at least 200-400 mg. per 500-900 gm. guinea-pig, and to prohibitively large doses for human beings while in the above experiments reported only 25 mg. were used daily. The mice used by Robertson were also normal, and taking into consideration the difference in dosage, the fact that different animals were used, and that these animals were sensitized to tuberculosis, it is easily appreciated that while his experiments were productive of results these experiments, differing as they do, are in no way contradictory to his findings—the conditions being different. From a practical standpoint, however, it would be impossible to use in tuberculosis a dose of tethelin even approaching that used in the foregoing experiments. For this reason and unless the human being is much more susceptible in response toward tethelin it would hardly seem that tethelin in practical doses can have any effect by analogy on tuberculosis as found in the human being. The foregoing experiments also do not rule out the possibility of tethelin in very large doses having a favorable action on the tubercle, since this was not tried. It may someday be possible to produce tethelin synthetically or to further concentrate the wound-healing principle which might still make it practically applicable as an indirect therapeutic agent in tuberculosis. At present, however, its administration can hardly be justified as a therapeutic agent.

SUMMARY

Tethelin the active principle of the anterior lobe of the pituitary, administered subcutaneously in 25 mg. doses on alternate days for 18 days before and during early infection to tuberculous guinea-pigs, infected with virulent human tubecle bacilli, had no appreciable effect on the progress of the tuberculosis or on the duration of life of these animals.

Tethelin administered subcutaneously in 25 mg. doses daily to guinea-pigs sensitized to tuberculosis by dead and living (avirulent) human tubercle bacilli had no appreciable effect on the development, recession, or rupture of intracutaneous tubercles produced by dead human tubercle bacilli nor on deep puncture wounds of the skin in these animals.